- Creditor, M. C., Bevans, M., Mundy, W. L., and Ragan, C. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, 74, 245.
 Gemzell, C. A. (1953). *J. clin. Endocr.*, 13, 898.
 Gold, J. J. (1957). *Ibid.*, 17, 296.
 Jailer, J. W. (1956). *Bull. Sloane Hosp. Wom. (N.Y.)*, 3, 82.
 McKay, E., Assali, N. S., and Henley, M. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, 95, 653.
 Poidevin, L. O. S., and Bockner, V. Y. (1958). *J. Obstet. Gynaec. Brit. Emp.*, 65, 278.
 Robinson, H. J., Bernhard, W. G., Grubin, H., Wanner, H., Sewekow, G. W., and Silber, R. H. (1955). *J. clin. Endocr.*, 15, 317.
 Schwarz, O. H., Paddock, R., and Bortnick, A. H. (1938). *Amer. J. Obstet. Gynec.*, 36, 962.
 Siegel, I. (1952). *Ibid.*, 64, 301.
 Venning, E. H. (1946). *Endocrinology*, 39, 203.

DIABETES INSIPIDUS ASSOCIATED WITH TUBERCULOUS MENINGITIS

BY

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Diabetes insipidus is a rare syndrome of water-balance disturbance characterized by the excretion of excessive quantities of urine with resultant polydipsia.

Apart from heredity, the common causes of diabetes insipidus are trauma, encephalitis, brain tumours (such as gliomata, craniopharyngiomata, meningiomata, or chromophobe adenomata of the pituitary gland), syphilis, Hand-Schüller-Christian disease or xanthoma, and cerebrovascular accidents (Fink, 1926, 1928; Warkany and Mitchell, 1939; Biggart, 1935; Wyllie, 1943; Jones, 1944; Soffer, 1956). Meningitis is an extremely rare cause. In Fink's (1928) series tuberculoma and tuberculous meningitis comprised 5% of cases, with non-syphilitic inflammatory conditions 9%. Soffer (1956), in a review of 160 cases collected from the literature, states that inflammatory diseases (that is, encephalitis, meningitis, tuberculosis, and syphilis) accounted for 31 cases (20%). Jones (1944), observing 42 cases, mentions only one associated with meningitis; and Hagenbach (1883) reported one case of diabetes insipidus resulting from tuberculous meningitis. Healy (1935) gave an account of a case occurring in a child of 2½ years with miliary tuberculosis and basal meningitis. Acheson and Smith (1958) described a case of tuberculous meningitis in which diabetes insipidus occurred five years after the onset of the infection. Lorber (1958) reported a similar association, and briefly reviewed 11 other cases which appeared mainly in the European literature.

In view of the rare association of diabetes insipidus with meningitis, a further case is here presented.

Case Report

A 5-year-old Bantu girl was admitted to the paediatric unit, Coronation Hospital, on October 12, 1956, with the complaint of headache for one month, a painful and stiff neck for three weeks, prominence of the eyes, and thirst and polyuria associated with marked weight loss. There had been no previous illnesses and the family history was non-contributory. The child's developmental history was normal.

Examination revealed a thin, undernourished child lying curled up in bed, very irritable and uncooperative. Stiffness of neck and back was present, and a marked proptosis of both eyes with bilateral sixth-nerve palsies was noted. Fundoscopic examination revealed temporal pallor of both

disks. Reflexes were equal but accentuated, and the plantar response was normal on both sides. Tone was normal. The pulse rate was 110, respirations 28, temperature 99° F. (37.2° C.), and blood pressure 100/60 mm. Hg.

The cerebrospinal fluid showed numerous pus cells and lymphocytes, but no bacteria were detected on direct or cultural examination; protein, 230 mg./100 ml.; chloride (as NaCl), 640 mg./100 ml.; sugar, 27 mg./100 ml. The leucocyte count was 11,000/c.mm. Urinalysis was normal. Patch test for tuberculosis was negative (activity equal to 0.0001 ml. (0.1 mg.) of Old Tuberculin). Radiological examination of the heart and skull showed nothing abnormal; the pituitary fossa and sinuses were normal; the lung films showed hilar adenopathy with perifocal pneumonia (Fig. 1). While awaiting the cultural examination of the C.S.F. the patient was treated with soluble penicillin, 250,000 units, and sulphadiazine, 0.5 g. every six hours.

She remained febrile, with temperatures rising to 102° F. (38.9° C.). Polyuria and polydipsia continued, with daily variation in quantity. Re-examination of the C.S.F. showed 60 polymorphonuclears and 45 lymphocytes per c.mm. and protein 1,700 mg./100 ml., with insufficient fluid for sugar and chloride estimations. As the patient's condition had deteriorated, with persistence of the pyrexia, sulphadiazine was stopped on October 19 and tetracycline, 62.5 mg., was given every six hours. Thereafter the proptosis receded and the temperature started to settle. The C.S.F., however, showed no essential change.

On November 11 a Mantoux test with purified protein derivative (second strength) was positive and treatment was altered to intramuscular streptomycin sulphate, 0.5 g. daily, and oral isoniazid, 0.1 g. three times daily. Thereafter the child showed steady improvement, with gradual return of the C.S.F. to normal. The bilateral sixth-nerve palsies disappeared, but the polyuria and polydipsia continued. On December 8 the patient became dehydrated and required intravenous fluid therapy. Aqueous "pitressin," 0.25 ml. eight-hourly, was then started with dramatic decrease in her fluid intake and urinary output, which fell to near-normal values. She rapidly began to gain weight. Aqueous pitressin was changed to pitressin tannate in oil, 2.5 units daily, on January 16, 1957. She was finally stabilized on alternating daily doses of 2.5 and 5 units. Pitressin therapy was discontinued on March 6, 1957. The fluid intake and urinary output immediately rose.

Further Investigations

Weight 32½ lb. (14.6 kg.); height 38 in. (96.5 cm.); span 39 in. (99 cm.); lower segment 18 in. (45.5 cm.), ratio upper to lower segments 1:0.9; head circumference 20 in. (51 cm.); chest circumference 21½ in. (54.5 cm.); abdominal circumference 23½ in. (59.5 cm.). Blood urea, 25 mg./100 ml.; plasma chloride, 103 mEq/l.; CO₂ combining power, 21 mEq/l.; serum calcium, 5 mEq/l.; serum sodium,

FIG. 1.—Radiograph of chest (right lateral) on October 12, 1956, showing hilar adenopathy and perifocal pneumonia in the right lower lobe.

133 mEq/l.; serum potassium, 5.3 mEq/l.; plasma cholesterol, 210 mg./100 ml.

Urine: pH 7.4, chemically and microscopically normal, maximum concentration 1007; urinary urea content, 240 mg./100 ml.; urinary chloride excretion (as NaCl), 1.7 g./l. (3.57 g. in 24 hours). The urea clearance test gave abnormally low figures on two occasions (24% and 23%). On treatment with pitressin, it rose to 51%. Phenolsulphonphthalein excretion test: total excretion after two hours 47.1%; on treatment 77.9%.

Intravenous pyelograms revealed normal kidneys. Hickey-Hare test (see below): with the infusion of hypertonic saline, the urinary flow increased; it fell sharply when 4 units of aqueous pitressin was given by intramuscular injection. In Fig. 2 the patient's response is contrasted with that of a normal child two years older than she.

In the patient the first infusion of hypertonic saline resulted in *no* significant reduction of urinary flow, and for this test to be negative there should be a reduction of at least 75%. She showed, rather, a rise in urinary flow, which we felt was significant in itself, and this was reduced only with the administration of pitressin. This was in complete contrast to the curve obtained in the normal subject and what was described by Hickey and Hare (1944) and Carter and Robbins (1947). We felt justified, therefore, in accepting this as a positive test.

Pitressin tannate was restarted on March 28, 1957, with the dose on which the patient was previously stabilized. There was again a dramatic reduction in urinary output

FIG. 2.—Hypertonic saline infusion tests.

and fluid intake. Five days later, however, the dose had to be reduced to 2.5 units daily, as abdominal pain developed and the urinary output had fallen markedly. On the latter dose she was well maintained and had a daily urinary output of 1–1.5 litres. She was discharged from hospital on April 26 to the Margaret Ballinger Home for Bantu Children, still receiving streptomycin and isoniazid.

Progress

Treatment with streptomycin and isoniazid was continued until October. She was then well, but still required pitressin daily to control her urinary output, which had been falling steadily. Pitressin was therefore reduced to 2.5 units on alternate days and subsequently was stopped completely in an effort to wean the child from the hormone. Though the immediate result was promising, she relapsed and was readmitted on March 18, 1958. A full clinical examination was completely normal.

The daily fluid intake and urinary output varied greatly from day to day, the former usually 5–9 litres and the latter 3–6 litres (Fig. 3). Haemoglobin, 16.0 g./100 ml.; P.C.V.,

43%; M.C.H.C., 37%; leucocytes, 9,700/c.mm. Cerebrospinal fluid: 3 lymphocytes/c.mm.; protein, 15 mg./100 ml.; chloride, 569 mg./100 ml.; sugar, 45 mg./100 ml. Serum electrolytes and urinalysis revealed no abnormality. Urine concentration test, 1007 (after 16 hours). Urea clearance test, 81% of average normal renal function (corrected for body size). Phenolsulphonphthalein excretion test, 68.9%

FIG. 3.—Fluid intake and urinary output chart.

excretion (after two hours). The Hickey-Hare test again showed an increased urinary output with the infusion of hypertonic saline solution, showing that the patient was suffering from pitressin-deficient (neurogenic) diabetes insipidus (Fig. 2). F.S.H., 6–12 mouse units/24 hours; 17-ketosteroids, 2.9 mg./24 hours; 17-hydroxycorticoids, 1 mg./24 hours. The glucose-tolerance curve was abnormally low on two occasions, with a fasting level of 70 mg./100 ml.

On April 16 pitressin tannate, 2.5 units daily, was recommenced, and by the following day she had gained 2 lb. (0.9 kg.) in weight but complained of abdominal pain. Two days later she showed signs of water intoxication (headache, nausea, and vomiting, followed by weakness, irritability, and coma); she was incontinent and oliguric. Pitressin was stopped, and in an effort to promote a diuresis 10 ml. of 50% dextrose in water was given intravenously with good effect. By next morning she had improved and was kept under observation for a further period without treatment. In July the use of daily nasal insufflations of pitressin powder (capsules containing 30 units of antidiuretic substance) at 9 a.m. produced an immediate response. The urinary output fell to 2–3 litres daily, but excessive nocturia persisted. The addition of an insufflation at 9 p.m. caused the urinary output to fall to 700–900 ml. daily. She has since been well controlled on this regime, and there have been no untoward effects.

Discussion

As pointed out by Lorber (1958), the site of maximal infection and exudate in tuberculous meningitis is the basal cisterns. The lesion may cause endarteritis and vascular thromboses, with resultant softening and destruction of the surrounding brain tissue, and diabetes insipidus may occur as a result of the anatomical proximity of the pituitary gland and the hypothalamic-hypophyseal pathways.

In the observed onset of diabetes insipidus, as in experimental hypophysectomy in animals, or following operative procedures such as the removal of craniopharyngioma, the onset of polyuria and polydipsia is of short duration, lasting approximately five days; an interphase of 10–14 days of normal fluid intake and urinary output follows. This is then replaced by permanent polyuria and polydipsia. The cause of the interphase is not yet fully understood, but two theories have been

postulated. The first suggests that there is a temporary secretion of pitressin by the cells of the median eminence and posterior lobe of the hypophysis, while the second theory states that there is a release of stored anti-diuretic hormone (A.D.H.) from the degenerating posterior lobe. Mudd *et al.* (1957) have shown that sectioning of only the hypothalamic-hypophysial pathway results in diabetes insipidus with interphase, whereas the interphase does not occur if all the vasopressor-secreting tissue is removed—that is, sectioning of the hypothalamic-hypophysial tract with hypophysectomy. Lipsett and Pearson (1956) believe that, at equal solute loads, the severity of the diabetes insipidus depends on the level of stalk section and a preservation of a variable portion of the pars nervosa.

In the case presented here, the symptoms were characteristic: polydipsia was outstanding, as is usual in children. They have been seen to drink water from flower bowls or their own urine to relieve their thirst. Enuresis may occur as the first symptom in children where bladder control has been previously established. In adults the polyuria and the need for fluid may be so great as to interfere with work and sleep. If fluid is withheld in these cases, dehydration rapidly ensues, with headache, fatigue, irritability, muscular pains, weight loss, and tachycardia. Cardiovascular collapse may result. The urine is pale, the specific gravity being between 1001 and 1008 and rarely above 1010. The renal-function tests are usually within normal limits, but the effective plasma clearance may be decreased. This is thought to be due to an impairment in the excretory function of the tubular cells which is restored under the influence of repeated administration of posterior pituitary extract (Winer, 1942). The diagnosis of diabetes insipidus was confirmed by the typical response to standard quantities of hypertonic saline and pitressin. Fig. 2 shows the continued excretion of excessive quantities of urine (failure of the hypophysis to liberate A.D.H.) and the decrease following pituitrin which excludes renal disease (or pitressin-resistant diabetes insipidus). The tuberculous nature of the meningitis was indicated by the active tuberculous focus in the chest, development of tuberculin skin hypersensitivity, and a suggestive cerebrospinal fluid, despite the failure to isolate the mycobacteria. The excellent response to antituberculous therapy, with complete resolution of the meningitis and the subsequent demonstration of calcification in the hilar glands, established this aetiology. The lesion produced by the meningitic process is likely to be situated in the hypothalamic-hypophysial tracts or in the hypothalamic nuclei. It seems unlikely that a lesion occurring in the region of the pituitary gland would produce total destruction of the posterior lobe without affecting the anterior lobe as well. The absence of any signs of hypopituitarism in this patient excludes the latter possibility.

This case exhibits an unusual feature in that the glucose-tolerance test showed a low fasting sugar and an extremely low curve; the usual result is a normal curve or one resembling that of diabetes mellitus. Gibson *et al.* (1927), investigating blood-sugar curves in seven cases of diabetes insipidus, showed persistently increased blood sugars with curves similar to those of diabetes mellitus in six, while only one had an abnormally flattened curve. Bauer (1954), however, in a general survey of hypothalamic disease, found 3 patients out of 10 with flattened curves, and 3 who had a delayed return of the blood sugar to normal. There

has been no evidence of malabsorption, and the cause of the flattened curve is not fully understood.

Summary

A case of diabetes insipidus associated with tuberculous meningitis in a child of 5 years is reported. Treatment with nasal insufflation of powdered posterior pituitary extract successfully controlled the patient's polyuria.

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REFERENCES

- Acheson, R. M., and Smith, H. V. (1958). *Quart. J. Med.*, **27**, 83.
 Bauer, H. G. (1954). *J. clin. Endocr.*, **14**, 13.
 Biggart, J. H. (1935). *Brain*, **58**, 86.
 Carter, A. C., and Robbins, J. (1947). *J. clin. Endocr.*, **7**, 753.
 Fink, E. B. (1926). *Endocrinology*, **10**, 317.
 — (1928). *Arch. Path. (Chicago)*, **6**, 102.
 Gibson, R. B., Magers, E. J., and Dulaney, H. (1927). *Endocrinology*, **11**, 341.
 Hagenbach, E. (1883). *Jb. Kinderheilk.*, **19**, 214. Quoted by T. B. Fitcher, *Med. Clin. N. Amer.*, 1935, **18**, 1597.
 Healy, J. W. (1935). *Brit. J. Child. Dis.*, **32**, 275.
 Hickey, R. C., and Hare, K. (1944). *J. clin. Invest.*, **23**, 768.
 Jones, G. M. (1944). *Arch. intern. Med.*, **74**, 81.
 Lipsett, M. B., and Pearson, O. H. (1956). *Med. Clin. N. Amer.*, **40**, 773.
 Lorber, J. (1958). *Arch. Dis. Childh.*, **33**, 315.
 Mudd, R. H., Dodge, H. W., Clarke, E. C., and Randall, R. V. (1957). *Proc. Mayo Clin.*, **32**, 99.
 Soffer, L. J. (1956). *Diseases of the Endocrine Glands*, 2nd ed., p. 170. Lea and Febiger, Philadelphia.
 Warkany, J., and Mitchell, A. G. (1939). *Amer. J. Dis. Child.*, **57**, 603.
 Winer, N. J. (1942). *Arch. intern. Med.*, **70**, 61.
 Wyllie, W. G. (1943). *Proc. roy. Soc. Med.*, **36**, 581.

CLINICAL TRIAL OF FURAZOLIDONE IN TREATMENT OF DIARRHOEA

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Medical practice in Bombay is not always comparable with that in the United Kingdom. The standard of living and the conditions under which patients have to be treated are very different from those seen in Western countries. Because of these conditions gastro-enteritis looms large as one of our main therapeutic problems. Another factor is that the continuous advances in the treatment of infectious diseases have produced diverse problems, prominent amongst which is the appearance of extremely virulent pathogenic bacteria which have become resistant to all antibiotics and sulphonamides. The West Bengal Government has warned medical practitioners against uncontrolled or inefficient use of antibiotics, which, if not checked, would increase the incidence of resistant strains of bacteria still further.

Apart from the expense and inconvenience of administering antibiotics and sulphonamides I have found resistant strains develop very readily. This is especially so with *Micrococcus pyogenes* and *Micrococcus aureus*. *Candida albicans*, *Pseudomonas aeruginosa*, *Proteus*, and enterococci are also involved. The necessity for finding a drug which does not produce bacterial resistance and is cheap and easy to administer